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Diagnostic Performance of Cerebroplacental Ratio Thresholds at Term for Prediction of Low Birthweight and Adverse Intrapartum and Neonatal Outcomes in a Term, Low-Risk Population

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Keywords

Cerebroplacental ratio · Cerebroumbilical ratio · Low birthweight · Small for gestational age · Growth restriction · Cesarean section · Intrapartum fetal compromise · Fetal distress · Neonatal outcome

Abstract

Objectives: To investigate the screening performance and best threshold centile (5th vs. 10th) of the cerebroplacental ratio (CPR) in low-risk, term pregnancies to predict low birthweight and adverse intrapartum and neonatal outcomes in a term, low-risk population. ***Methods:*** This was a blinded, prospective, cross-sectional study of low-risk singleton pregnancies at term. Women attended fortnightly from 36 weeks for CPR and estimated fetal weight assessment. Intrapartum and neonatal outcomes were recorded. Primary outcomes assessed were low birthweight, cesarean section for intrapartum fetal compromise, and composite adverse neonatal outcome. ***Results:*** A total of 483 women participated in the study. The CPR 10th centile (1.48) threshold resulted in the best screening performance. Sensitivities for low birthweight, cesarean section for intrapartum fetal compromise, and composite adverse neonatal outcome of 41.9, 61.1, and 38.3% were achieved for false-positive rates of 17.7, 17.7, and 15.2%, respectively. The corresponding areas under the receiver operating characteristic curves were 0.62, 0.72, and 0.62. ***Conclusion:*** The CPR 10th centile resulted in the best screening performance, although this would be considered fair at best. The CPR 10th centile may be useful as part of a risk stratification tool for prediction of low birthweight and adverse intrapartum and neonatal outcomes.

Introduction

Growth-restricted neonates are known to be at increased risk of intrapartum and neonatal complications and longer-term neurological sequelae. Compared to their appropriately grown counterparts, these fetuses have a five times greater risk of stillbirth, particularly when growth restriction is unrecognised antenatally [1]. Recently there has been debate regarding the definition of fetal growth restriction with some authors suggesting a more appropriate definition of fetal growth restriction would be the presence of a low cerebroplacental ratio (CPR) rather than solely fetal weight [2–5]. This is because a definition based purely on size may fail to identify a fetus whose estimated weight is >10th centile but

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may indeed have suboptimal growth and thus a failure to reach its genetic growth potential. Additionally it may also classify constitutionally small fetuses as being growth restricted. In practice, however, clinical identification of a small-for-gestational-age fetus is often the primary screening approach for growth restriction. Conventionally, small fetuses are first suspected by abdominal palpation and/or symphyseal-fundal height assessment before more objective estimation of fetal weight by ultrasound. However, clinical assessment is known to have poor sensitivity [6] and ultrasound estimation of fetal weight can have significant error [7], particularly at extremes of fetal weight and gestation. Universal and selective ultrasound screening have shown relatively unimpressive detection rates (sensitivity 57 and 20%, respectively) for the identification of the small-for-gestational-age fetus [8]. Furthermore, various large systematic reviews [6, 9] suggest no improvement in clinical outcomes when universal sonography is applied, with recommendations for high-quality research to address this need. Therefore, a more accurate screening approach to identify the growth-restricted fetus in apparently uncomplicated pregnancies is needed.

The CPR is currently the focus of much research to identify fetuses that fail to reach their genetic growth potential and/or are at increased risk of perinatal complications. Different CPR thresholds have been suggested for screening in this context, particularly the CPR 5th and 10th centiles [10–13]. However, to our knowledge, there is no prospective data examining the performance of these thresholds to identify pregnancies at risk of these complications in a low-risk population at term.

The primary aim of this study was to prospectively assess the performance characteristics of the fetal CPR 5th and 10th centiles to screen for perinatal complications in term, low-risk pregnancies and determine the most appropriate of these thresholds. The secondary aims were to investigate the screening performance of the CPR 5th–50th centiles, compare the CPR values, and to investigate the predictive value of the CPR 10th centile compared to estimated fetal weight for babies with perinatal complications.

Methods

This was a prospective, observational study conducted at the Mater Mothers' Hospitals in Brisbane, Australia from May 2014 to August 2016. Women with uncomplicated singleton pregnancies who were planning a vaginal birth were recruited during routine antenatal appointments in their third trimester of pregnancy. Pregnancies were dated from first-trimester ultrasound. Study protocol approval was granted by the institute's committees for ethics and governance on human research prior to study commencement (Ref. No. HREC/13/MHS/173).

Women provided informed signed consent at enrolment and underwent fortnightly ultrasounds from 36 weeks until delivery. At each visit, the umbilical artery pulsatility index (PI) and middle cerebral artery (MCA) PI were calculated from three consecutive waveforms during fetal quiescence using an automated trace of the spectral Doppler waveform. The CPR was calculated as a simple ratio of the MCA PI to the umbilical artery PI as previously described [14]. The last CPR prior to delivery is reported and used for all analyses. The CPR reference centiles were calculated from women in the study that birthed by spontaneous vaginal delivery with no intrapartum fetal compromise (IFC) and an absence of the composite adverse neonatal outcome (ANO). Reference centiles were not adjusted for gestation. Women and clinicians were blinded to the ultrasound results, except if severe oligohydramnios (deepest pocket <1 cm), absent or reversed end diastolic flow in the umbilical artery, or malpresentation were identified.

Birthweight, mode and indication for birth, and neonatal outcomes were recorded within 72 h of birth. Decision for operative delivery (instrumental or cesarean section [CS]) for fetal compromise was recorded as that made contemporaneously by the treating obstetric team. Classification of fetal heart rate (FHR) patterns was based on guidelines from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists [15], which are very similar to those published by the National Institute of Clinical Excellence [16] in the United Kingdom and American College of Obstetricians and Gynecologists [17] in the United States. Mode of birth was divided into five categories based upon the primary indication for delivery: spontaneous vaginal delivery with no fetal compromise, instrumental (with or without fetal compromise), and CS (with or without fetal compromise). Umbilical cord gases were performed at the discretion of the attending clinical team in accordance with guidelines at our institution.

Three primary outcomes were assessed; low birthweight (<5th and <10th centile), CS for IFC, and a composite ANO (pH ≤7, base excess ≤–12, and/or lactate >6 mmol/L, Apgar score ≤5 at 5 min, and/or neonatal intensive care unit [NICU] admission). Birthweight centile was classified according to an appropriate population standard [18]. Secondary outcomes were IFC, acidosis at birth (cord artery pH ≤7, base excess ≤–12, and/or lactate >6 mmol/L), low Apgar score (≤5 at 5 min), and NICU admission.

Statistical Analysis

Screening performance was assessed for the CPR <5th and <10th centiles and the CPR 5th–50th centiles in 5-centile increments for the primary outcomes.

Comparisons between continuous variables for the various outcomes were assessed using Wilcoxon rank-sum test and Kruskal-Wallis rank-sum test with post hoc Bonferroni correction for multiple comparisons, as appropriate. Associations between categorical variables were assessed using Pearson χ^2 test and Fisher exact test, as appropriate. Summary statistics for normally distributed continuous variables are reported as mean (standard deviation [SD]), non-normally distributed variables are reported as median (interquartile range [IQR]), and categorical variables as *n* (%). Logistic regression was applied to generate odds ratios (OR) and receiver operating characteristic (ROC) curves for the specified

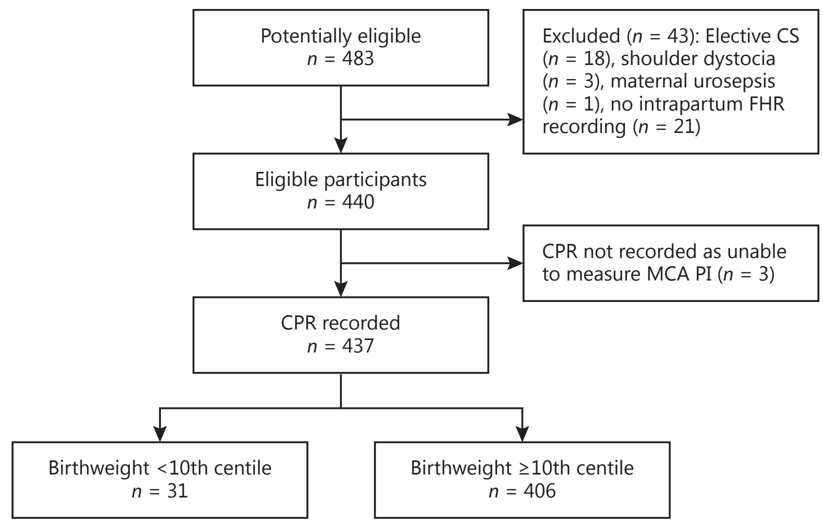

Fig. 1. Participant flow diagram. CS, cesarean section; FHR, fetal heart rate; CPR, cerebroplacental ratio; MCA PI, middle cerebral artery pulsatility index.

outcomes to assess screening performance. p values <0.05 were considered significant and all tests were two-tailed. The statistical software package Stata®, Release 13, for Windows (StataCorp LP, College Station, TX, USA) was used for statistical analysis.

Results

During the study period, 483 women enrolled in the study, of which 43 were excluded for various reasons (Fig. 1). These included 18 (3.7%) who underwent elective CS, 21 women (4.3%) who did not have intrapartum FHR monitoring, and three women (0.7%) because of inability to measure the MCA PI. In addition, as this study was designed to assess the association between IFC precipitated by placental dysfunction rather than maternal conditions or birth trauma, one woman (0.2%) was excluded due to severe urosepsis and three women (0.6%) were excluded as birth was complicated by severe shoulder dystocia. The final study cohort thus comprised of 437 women (Table 1). Umbilical artery cord gas analysis was performed in 55.4% (242/437) of women.

Eleven (2.5%) and 31 women (7.1%), respectively, delivered infants with birthweights <5th and <10th centiles. Eighteen women (4.1%) delivered infants with birthweights >90th centile. The CPR <10th centile threshold produced better screening performance than the CPR 5th centile for the three primary outcomes (Table 2). CS IFC achieved the greatest area (0.72) under the ROC (AUROC) curve of all outcomes. For birthweight <5th centile, birthweight <10th centile, and composite ANO, the AUROC curve was 0.63, 0.62, and 0.62, respectively. The CPR 5th and 10th centile values were 1.27 and 1.48, respectively.

Table 1. Participant demographics

Characteristics	Overall (n = 437)
Nulliparous	382 (87.4%)
Maternal age, years	29.8 (4.5)
Body mass index	22.6 (20.9–25.8)
Ethnicity	
Caucasian	269 (61.6%)
Oriental	77 (17.6%)
Indian	46 (10.5%)
Other	45 (10.3%)
Diabetes mellitus	35 (8.0%)
Chronic hypertension	1 (0.2%)
Cigarette smoker	41 (9.4%)
Assisted reproductive technology	11 (2.6%)
Gestational age at scan, weeks	38.4 (37.9–39.9)

Data are expressed as n (%), mean (SD), or median (IQR), as appropriate.

Sub-analysis of CPR centile for all cases of IFC (instrumental and CS) versus uncomplicated deliveries and the individual components of composite ANO (acidosis at birth, low Apgar score, and NICU admission) demon-

Table 2. Diagnostic performance of the cerebroplacental ratio 5th and 10th centiles for prediction of low birthweight, cesarean section for intrapartum fetal compromise, and composite adverse neonatal outcome

	Sensitivity, %	FPR, %	+LR	–LR	AUROC
BW <5th centile					
CPR 5th (1.27)	18.2 (3.2–50.9)	7.7 (5.2–10.3)	2.35 (0.4–7.13)	0.89 (0.53–1.05)	0.55 (0.43–0.67)
CPR 10th (1.48)	45.5 (18.3–75.1)	18.8 (15.1–22.5)	2.42 (0.94–4.17)	0.67 (0.30–1.01)	0.63 (0.48–0.79)
BW <10th centile					
CPR 5th (1.27)	19.4 (8.4–35.7)	7.1 (4.6–9.7)	2.71 (1.05–6.05)	0.87 (0.68–1.00)	0.56 (0.49–0.63)
CPR 10th (1.48)	41.9 (25.6–59.8)	17.7 (14.0–21.5)	2.37 (1.35–3.65)	0.71 (0.48–0.92)	0.62 (0.53–0.71)
CS IFC vs. all other					
CPR 5th (1.27)	33.3 (14.8–57.1)	6.9 (4.5–9.4)	4.82 (1.91–9.67)	0.72 (0.46–0.92)	0.63 (0.52–0.74)
CPR 10th (1.479)	61.1 (36.8–81.4)	17.7 (14.0–21.3)	3.46 (1.97–4.85)	0.47 (0.22–0.78)	0.72 (0.60–0.83)
Composite ANO					
CPR 5th (1.27)	17.3 (10.8–24.5)	5.9 (3.5–8.4)	2.93 (1.46–5.74)	0.88 (0.79–0.96)	0.56 (0.51–0.60)
CPR 10th (1.48)	38.3 (29.1–47.8)	15.2 (11.4–18.9)	2.45 (1.68–3.67)	0.73 (0.60–0.86)	0.62 (0.56–0.67)

FPR, false-positive rate; +LR, positive likelihood ratio; –LR, negative likelihood ratio; AUROC, area under the receiver operator characteristic curve; BW, birthweight; CPR, cerebroplacental ratio; CS IFC, cesarean section for intrapartum fetal compromise; composite ANO, composite adverse neonatal outcome (abnormal cord gases [umbilical artery pH ≤7.0, base excess ≤–12, and/or lactate >6 mmol/L], Apgar score ≤5 at 5 min, and/or neonatal intensive care unit admission).

strated that the best screening performance was again achieved at the CPR <10th centile. The AUROC curves for IFC, abnormal umbilical artery cord gases, low Apgar score, and NICU admission were 0.67, 0.60, 0.57, and 0.60, respectively.

Screening performance of the CPR 5th–50th centiles was performed in 5-centile increments for the primary outcomes (online supplementary Table i; available at www.karger.com/doi/10.1159/000477932).

Median CPR values were lower in low-birthweight babies, those delivered by CS IFC, and those with the composite ANO (Table 3). Babies delivered by CS IFC had the lowest CPRs of all delivery modes (1.41, IQR 1.23–1.80), whilst babies delivered by CS without compromise had the highest CPR values (1.97, IQR 1.70–2.22). Median CPR values were lower in babies who were delivered for IFC (CS or instrumental) compared to all other deliveries (1.50, IQR 1.33–1.89 vs. 1.9, IQR 1.61–2.23, respectively; $p < 0.0001$). Babies delivered without IFC (spontaneous vaginal or instrumental) had higher CPR values (1.86, IQR 1.59–2.23 and 1.93, IQR 1.61–2.23, respectively) than each category of operative delivery (instrumental or CS) for IFC (1.57, IQR 1.36–1.89 and 1.41, IQR 1.23–1.80, respectively).

Low-birthweight neonates represented a greater proportion of CS IFC deliveries and those with the composite ANO than their >10th centile birthweight counterparts. The CS IFC group had a greater proportion of babies with intrapartum FHR abnormalities and composite ANO than all other deliveries.

Babies with the composite ANO represented a greater proportion of fetuses with the CPR <10th centile, meconium-stained liquor, FHR abnormalities, operative delivery (instrumental or CS) for IFC, later gestation at birth, longer length of labour, lower birthweight, lower birthweight centile, and female sex than neonates delivered in good condition (Table 3). Conversely, spontaneous vaginal and CS births without IFC were associated with a lower incidence of composite ANO.

Estimated fetal weight centile was predictive of birthweight <10th centile but was not predictive of either CS IFC or composite ANO (Table 4). Conversely, a low CPR was associated with increased risk for both CS IFC and composite ANO (OR 7.33, 95% CI 2.75–19.50, $p < 0.001$ and 3.47, 95% CI 2.03–5.91, $p < 0.001$, respectively) (Table 4). Additionally, the CPR <10th centile was associated with increased risk of IFC (instrumental and CS deliveries) compared with other deliveries (OR 6.09, 95% CI 3.58–10.38, $p < 0.001$).

Discussion

The results of this study demonstrate that the CPR 10th centile produces the best diagnostic performance for the prediction of low birthweight, emergency CS IFC, and

Table 3. Intrapartum and neonatal outcomes by birthweight, cesarean section for intrapartum fetal compromise, and composite adverse neonatal outcome

Outcome	Overall (n = 437)	BW <10th centile			CS IFC			Composite ANO		
		yes (n = 31)	no (n = 406)	p	yes (n =18)	no (n = 419)	p	yes (n = 81)	no (n = 356)	p
CPR	1.84 (1.55–2.18)	1.59 (1.35–1.95)	1.86 (1.57–2.18)	0.01$^{\#}$	1.41 (1.23–1.8)	1.86 (1.57–2.18)	0.002$^{\#}$	1.74 (1.39–2.05)	1.87 (1.60–2.19)	0.003$^{\#}$
CPR <10th centile	85 (19.5%)	13 (41.9%)	18 (4.4%)	0.001^{+}	11 (61.1%)	7 (2.0%)	0.03^{+}	31 (38.3%)	54 (15.2%)	<0.001^{+}
Intrapartum										
Meconium liquor	114 (26.2%)	8 (25.8%)	106 (26.1%)	0.97^{+}	4 (22.2%)	110 (26.3%)	1.00^{+}	37 (32.5%)	77 (67.5%)	<0.001^{+}
FHR abnormalities	160 (36.6%)	16 (51.6%)	144 (35.5%)	0.07^{+}	17 (94.4%)	143 (34.1%)	<0.001^{+}	54 (66.7%)	106 (29.8%)	<0.001^{+}
Delivery outcome										
SVD – no IFC	223 (51.0%)	17 (54.8%)	206 (50.7%)	0.66^{+}	–	–	–	27 (12.3%)	196 (55.1%)	<0.001^{+}
Instrumental – no IFC	68 (15.6%)	2 (6.5%)	66 (16.3%)	0.20*	–	–	–	10 (14.7%)	58 (16.3%)	0.50^{+}
CS – no IFC	64 (14.7%)	1 (3.2%)	63 (15.5%)	0.04*	–	–	–	5 (6.2%)	59 (16.6%)	0.02*
Instrumental – IFC	64 (14.7%)	7 (22.6%)	57 (14.0%)	0.20^{+}	–	–	–	30 (37.0%)	34 (9.6%)	<0.001^{+}
CS – IFC	18 (4.1%)	4 (12.9%)	14 (3.5%)	0.03*	–	–	–	9 (11.1%)	9 (2.5%)	0.002^{+}
Gestational age at birth, weeks	40.0 (39.3–40.9)	40.4 (39.4–41.1)	40.0 (39.1–40.9)	0.20$^{\#}$	40.4 (39.6–40.9)	40 (39.1–40.9)	0.32$^{\#}$	40.6 (39.7–41.1)	40.0 (39.1–40.7)	0.001$^{\#}$
Labour duration, min	433 (284–623)	324 (252–432)	440 (296–627)	0.12$^{\#}$	720 (117–824)	432 (284–617)	0.59$^{\#}$	499 (354–740)	428 (273–593)	0.01$^{\#}$
Interval to birth, days	8 (5–12)	7 (4–9)	8.5 (3–13)	0.10$^{\#}$	7 (4–11)	8 (5–13)	0.36$^{\#}$	8 (5–11)	8 (5–13)	0.50$^{\#}$
Interval to birth, days (IOL excl)	8 (5–12)	8 (5–10)	8 (5–12)	0.71$^{\#}$	6 (4–11)	8 (5–12)	0.53$^{\#}$	9 (5–11)	8 (4–12)	0.48$^{\#}$
Neonatal outcomes										
BW, g	3,424 (3,130–3,732)	3,442 (3,160–3,740)	3,476 (3,180–3,760)	<0.001$^{\#\#}$	3,275 (2,970–3,540)	3,434 (3,130–3,737)	0.20$^{\#\#}$	3,364 (3,576–3,064)	3,464 (3,149–3,766)	0.02$^{\#\#}$
BW centile	45.0 (24.5–66.0)	6.0 (3.0–8.0)	48.0 (29.0–68.0)	<0.001^{+}	38 (15–48)	46 (25–66)	0.07^{+}	32 (16–52)	47 (27–69)	<0.001^{+}
Sex (male)	225 (51.5%)	15 (48.4%)	197 (48.5%)	0.98^{+}	8 (44.4%)	10 (55.6%)	0.72^{+}	29 (35.8%)	183 (51.4%)	0.01^{+}
Abnormal cord gases	72/242 (29.8%)	10/20 (50.0%)	62/222 (27.9%)	0.07^{+}	8 (47.1%)	64 (28.4%)	0.11^{+}	–	–	–
Low Apgar	3 (0.79%)	0 (0%)	3 (0.7%)	–	0 (0%)	3 (0.7%)	–	–	–	–
NICU admission	18/419 (4.3%)	3/30 (10%)	15/389 (3.9%)	0.13*	1 (6.3%)	17 (4.2%)	0.51*	–	–	–
Composite ANO	81 (18.5%)	11 (35.5%)	70 (17.2%)	0.01^{+}	9 (50%)	72 (17.2%)	0.002^{+}	–	–	–

Data presented as n (%) or median (IQR), as appropriate. CPR, cerebroplacental ratio; meconium liquor, meconium-stained liquor; FHR abnormalities, fetal heart rate suspicious or pathological; SVD, spontaneous vaginal delivery; IFC, intrapartum fetal compromise; CS, cesarean section; IOL excl, induction of labour cases excluded; BW, birthweight; abnormal cord gases, umbilical artery pH ≤7.0 and/or base excess ≤–12 and/or lactate >6 mmol/L; low Apgar, Apgar score ≤5 at 5 min; NICU, neonatal intensive care unit; composite ANO, composite adverse neonatal outcome (abnormal cord gases [umbilical artery pH ≤7.0, base excess ≤–12 and/or lactate >6 mmol/L], Apgar score ≤5 at 5 min, and/or NICU admission). $^{\#}$ Wilcoxon rank-sum test. $^{+}$ Pearson χ^2 test. * Fisher exact test. $^{\#\#}$ Student t test.

composite ANO. Additionally, the CPR 10th centile is a predictor of CS IFC and ANO.

Whilst the association between CPR and adverse intrapartum and neonatal outcomes has been shown previously in retrospective studies on unselected populations [2–5, 11, 19, 20], this prospective study demonstrates the association persists even in apparently low-risk term pregnancies prior to labour. Our findings suggests that it is possible to indirectly detect suboptimal placental function and predict some intrapartum complications in low-risk pregnancies using the CPR up to 2 weeks remote from birth at term. Our results show that fetuses with a CPR <10th centile are subject to an almost eight times greater risk of emergency CS IFC and a more than three times greater risk of ANO than those with a CPR ≥10th centile. Global screening performance of the CPR 10th centile was highest for CS IFC (AUROC 0.72), followed by birthweight <5th centile, birthweight

Table 4. Odds ratios for cerebroplacental ratio <10th centile for low birthweight, cesarean section for intrapartum fetal compromise, and composite adverse neonatal outcome

Outcome	Predictor	Odds ratio (95% CI)	p
BW <10th (n = 31)	CPR <10th centile	0.30 (0.14–0.64)	0.002
	EFW centile	1.09 (1.06–1.12)	<0.001
CS IFC (n = 18)	CPR <10th centile	7.33 (2.75–19.50)	<0.001
	EFW centile	0.99 (0.97–1.01)	0.41
Composite ANO (n = 81)	CPR <10th centile	3.47 (2.03–5.91)	<0.001
	EFW centile	0.99 (0.98–1.00)	0.06

BW, birthweight; CPR, cerebroplacental ratio; EFW, estimated fetal weight; CS IFC, cesarean section for intrapartum fetal compromise; ANO, adverse neonatal outcome.

<10th centile, and composite ANO (0.63, 0.62, and 0.62, respectively).

Although low birthweight is associated with late-onset growth restriction and intrapartum and neonatal complications [21–23], some babies born with birthweights above the 10th centile may have failed to reach their growth potential [11, 24] and are therefore also at risk of these complications. In our view, a 41.9% sensitivity for birthweight <10th centile based on CPR <10th centile may be reasonable and acceptable, given the imperfect presumption of birthweight as a reliable indicator of underlying placental insufficiency. In this context, the screening performance reported here based on the CPR in a low-risk population may be considered reasonable.

In contrast to other studies, our study reports a higher proportion of female fetuses with composite ANO than male fetuses (64.2 vs. 35.8%, p = 0.01, respectively). Other authors have reported higher proportions of male fetuses with perinatal complications such as non-reassuring intrapartum FHR patterns, operative delivery [25], preterm birth, low 5-min Apgar score, and neonatal death [26]. Sub-analysis suggests that the skew towards worse outcomes for female fetuses appear to be caused by the higher proportion of female fetuses (66.6 vs. 33.3%, p < 0.01, respectively) with abnormal cord gases, despite almost equal proportions of sexes (49.2 vs. 50.8%, respectively) tested. The reason for this finding is not immediately apparent from this study.

The strengths of this study are the prospective design and low-risk study cohort, which constitute most women at term in our institution and other high-income healthcare settings. These factors provide screening results reflective of the low-risk population, a group in which late-onset growth restriction is frequently unrecognised. Additionally, our findings show that as the CPR alone in low-risk term pregnancies has only fair to moderate screening performance, it may therefore be useful as a component of a broader risk stratification tool or algorithm.

The simplicity of a single CPR measurement in the final month of pregnancy is a strength of this study and lends itself to the incorporation of the CPR in a late-pregnancy scan. The diagnostic performance (sensitivity 61.1% and specificity 82.3%) for CS IFC, whilst not perfect, is nonetheless a significant improvement on what is currently available. Emergency operative birth for fetal distress is frequently traumatic for women and healthcare providers. These urgent deliveries are also a risk factor for ANO [27]. The sheer uncertainty of the possibility of IFC and some of its immediate and longer-term ramifications contributes to adverse perinatal outcomes globally. Prelabour identification of women at risk allows appropriate counselling and decisions about mode and place of birth to be made. These are likely to result in greater overall satisfaction for women and their healthcare givers and potentially improvement in perinatal outcomes.

We acknowledge the limitations of this study in that the overall prevalence of IFC in our population is relatively low and the cord gas analysis data are incomplete. The reason for this is that, in common with many other institutions in Australia, cord blood is only analysed when clinically indicated, i.e., if abnormal FHR patterns are present or delivery complications occur.

The performance of any screening test is very much influenced by the disease prevalence in the study population [28]. That is, when disease prevalence is high, the positive predictive value will also be high. Conversely, when disease prevalence is low, the positive predictive value will also be low, as is the case in this study. Whilst the positive predictive value of the CPR 10th centile in this study ranged from 5.9 to 36.5% for the various outcomes, its test performance is likely to be much higher in populations where the disease (suboptimal fetal growth) prevalence is higher, as seen in some low- and middle-income countries. The CPR in low-income healthcare settings would therefore be expected to yield better screening performance.

Dichotomising the CPR at a single threshold, such as above or below the 10th centile, is worthy of discussion. As the CPR is a continuous variable, selecting a single threshold means that severity of disease is not indicated by the risk assessment result. That is, extremely low CPR values produce the same adjusted risk as those just below the threshold, with mildly abnormal results. Similarly, values immediately above or below the threshold may in fact have similar clinical risk, although their adjusted risk will indicate entirely different risk profiles. Whilst ROC curves have been widely used to select a threshold at a value that optimises sensitivity and specificity, the simplification of results to either "normal" or "abnormal" has led to some authors advocating the use of likelihood ratios based on interval thresholds to more accurately reflect the data [29]. Interval thresholds provide more than two possible classification outcomes, thereby providing a graded reporting of risk dependent upon where a value fits within the intervals. This permits extremes of abnormal values to result in appropriately high positive likelihood ratios without dilution from less extreme abnormal results. Whilst there is merit in this approach, this has not been the approach of investigators. The majority of published studies investigating the utility of the CPR as a predictor for adverse outcomes have generally been threshold based using pre-specified thresholds such as CPR ≤1, CPR <5th, and CPR <10th centile [30].

Results from this study raise the question of what is an acceptable false-positive rate in screening for adverse perinatal outcome including stillbirth and neonatal death. Other population screening programs, such as prostate-specific antigen-based screening for prostate cancer and mammography for breast cancer, yield very high false-positive rates of 50–75% [31] and 42–61% [32], respectively. Clearly, screening for various cancers is tolerant of high false-positive rates and subsequent invasive testing. The CPR 10th centile produced a false-positive rate of <20% for the outcomes presented here. One could argue that if the CPR was used as a screening tool for adverse perinatal outcomes then a similar tolerance might be appropriate and indeed acceptable given the magnitude of potential adverse sequelae, both immediate (intrapartum hypoxic brain injury, stillbirth, serious neonatal morbidity) or late (neurodisability). In late pregnancy, management following an abnormal fetal well-being test usually involves timely delivery, either induction of labour or elective CS. Such intervention, when balanced against the risks of the previously described adverse outcomes, may be entirely reasonable. In view of this, we would suggest that a higher false-positive rate in the context of screening for adverse late pregnancy outcomes may be justified.

Disclosure Statement

The authors report no conflict of interest.

References

1 Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A: Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108.
2 Morales-Rosello J, Khalil A: Fetal cerebral redistribution: a marker of fetal compromise regardless of fetal size. Ultrasound Obstet Gynecol 2015;46:385–388.
3 Morales-Roselló J, Khalil A, Morlando M, Bhide A, Papageorghiou A, Thilaganathan B: Poor neonatal acid-base status in term fetuses with low cerebroplacental ratio. Ultrasound Obstet Gynecol 2015;45:156–161.
4 Khalil AA, Morales-Rosello J, Elsaddig M, Khan N, Papageorghiou A, Bhide A, Thilaganathan B: The association between fetal Doppler and admission to neonatal unit at term. Am J Obstet Gynecol 2015;213:57.e51–e57.
5 Khalil AA, Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B: Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? Am J Obstet Gynecol 2015;213:54–56.
6 National Institute of Health and Care Excellence: The investigation and management of the small-for-gestational-age fetus (green-top guideline No. 31). London, NICE 2014, 2016.
7 Dudley NJ: A systematic review of the ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol 2005;25:80–89.
8 Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS: Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet 2015;386:2089–2097.
9 Bricker L, Medley N, Pratt JJ: Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev 2015:CD001451.
10 Odibo AO, Riddick C, Pare E, Stamilio DM, Macones GA: Cerebroplacental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction: evaluating the impact of using gestational age-specific reference values. J Ultrasound Med 2005;24:1223–1228.

11 Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B: Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. Ultrasound Obstet Gynecol 2014;43:303–310.
12 Prior T, Mullins E, Bennett P, Kumar S: Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. Am J Obstet Gynecol 2013;208:124.e121–124.e126.
13 Baschat AA, Gembruch U: The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol 2003;21:124–127.
14 Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A: Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. Obstet Gynecol 1992;79:416–420.
15 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists: Intrapartum fetal surveillance. Clinical guideline (third edition), 2014, 2016.
16 National Institute of Health and Care Excellence: Intrapartum Care: Interpretation of Cardiotocograph Traces (NICE guideline cg190). London, NICE, 2014, 2015.
17 American College of Obstetricians and Gynecologists: ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol 2009; 114:192–202.
18 Fenton TR, Kim JH: A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013; 13:59.
19 Khalil A, Morales-Roselló J, Townsend R, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B: Value of third-trimester cerebroplacental ratio and uterine artery Doppler indices as predictors of stillbirth and perinatal loss: cerebroplacental ratio, uterine artery Doppler and stillbirth. Ultrasound Obstet Gynecol 2016;47:74–80.
20 Triunfo S, Crispi F, Gratacos E, Figueras F: Prediction of delivery of small-for-gestational-age neonates and adverse perinatal outcomes by fetoplacental Doppler at 37 weeks' gestation. Ultrasound Obstet Gynecol 2017; 49:364–371.
21 Doctor BA, O'Riordan MA, Kirchner HL, Shah D, Hack M: Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. Am J Obstet Gynecol 2001;185:652–659.
22 Parra-Saavedra M, Simeone S, Triunfo S, Crovetto F, Botet F, Nadal A, Gratacos E, Figueras F: Correlation between histological signs of placental underperfusion and perinatal morbidity in late-onset small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 2015;45:149–155.
23 McCowan L, Horgan RP: Risk factors for small for gestational age infants. Best Pract Res Clin Obstet Gynaecol 2009;23:779–793.
24 Prior T, Paramasivam G, Bennett P, Kumar S: Are babies that fail to reach their genetic growth potential at increased risk of intrapartum fetal compromise? Ultrasound Obstet Gynecol 2015;46:460–464.
25 Sheiner E, Levy A, Katz M, Hershkovitz R, Leron E, Mazor M: Gender does matter in perinatal medicine. Fetal Diagn Ther 2004;19: 366–369.
26 Weng YH, Yang CY, Chiu YW: Neonatal outcomes in relation to sex differences: a national cohort survey in Taiwan. Biol Sex Differ 2015;6:30.
27 Grace L, Greer RM, Kumar S: Perinatal consequences of a category 1 caesarean section at term. BMJ Open 2015;5:e007248.
28 Grimes DA, Schulz KF: Uses and abuses of screening tests. Lancet 2002;359:881–884.
29 Brown MD, Reeves MJ: Interval likelihood ratios: another advantage for the evidence-based diagnostician. Ann Emerg Med 2003; 42:292–297.
30 DeVore GR: The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol 2015;213:5–15.
31 Ilic D, O'Connor D, Green S, Wilt TJ: Screening for prostate cancer: an updated Cochrane systematic review. BJU Int 2011;107:882–891.
32 Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, Davidson B, Mongtomery RC, Crowley MJ, McCrory DC, Kendrick A, Sanders GD: Benefits and harms of breast cancer screening: a systematic review. JAMA 2015;314:1615–1634.